Remarks / Arguments

Claims 1-7, and 12 -16 are pending in this application. Claims 9-11 were canceled previously. Claim 8 has been canceled in this response. Claims 1, 12, and 13 are being amended. New claims 14-16 are now being added. No new matter has been added.

New claims 14-16 and the amendment to claim 13 are supported by the text at page 4, lines 17-21.

Claim Rejections - 35 U.S.C. § 103

Claims 1-8, 12, and 13 were rejected under 35 U.S.C. §103 as being unpatentable over Jenkins *et al.* (EP 0 205 282 B1) or Jenkins *et al.* (U.S. Pat. No. 4,940,587) in view of Arwidsson *et al.* (U.S. Pat. No. 5,783,215).

Preliminary comments

In discussing the Jenkins reference, the examiner uses the terms "oral pharmaceutical composition", and "oral administration dosage forms", without making the distinction that in Jenkins, "oral" means "for use in the mouth". Jenkins' tablets are not intended to be ingested.

The examiner states that it is unclear whether Jenkins teaches the different degrees of molar substitution, makes the assumption that the degree of molar substitution is different in Jenkins and the present claims, and concludes that it is deemed obvious to one of ordinary skill in the pharmaceutical art to obtain a suitable degree of molar substitution through routine or manipulative experimentation to obtain the best possible results. Jenkins does not discuss the degree of molar substitution of the water soluble hydroxyalkyl cellulose he employs. The examiner has cited no art indicating anything about how the degree of molar substitution of the water soluble hydroxyalkyl cellulose might be expected to affect its properties, and has instead

simply concluded that the selection of this parameter is within the ordinary skill of the art. It is deemed that this conclusion is without any basis and is therefore premature.

With respect to the concentration of the cellulose, the examiner states that Jenkins teaches that the concentration is preferable between 2% and 15 % (referring to page 3, lines 7-8), and does not teach the applicants' claimed range of 40-95%. The applicants would clarify that the Jenkins text referred to by the examiner is in the EP 205,282 Jenkins reference and relates to the extragranular adhesive cellulose (the adhesive coating, which is preferably HPC). The water soluble hydroxyalkyl cellulose employed in the granule matrix is also used at a level of 2-15 % by weight of the total dosage form weight. The examiner states that Jenkins clearly teaches the same ingredients for a similar intended purpose and therefore the expected results would also be the same. In this the examiner is incorrect. Jenkins teaches that the extragranular adhesive cellulose (the adhesive coating) is for improved adhesion to the mucosa, while the water soluble hydroxyalkyl cellulose of the matrix is to control the release of the drug from the composition. Furthermore, Jenkins allows the two celluloses to be the same, but his preferred materials for the coating and the matrix are different. The examiner concludes that the applicants' claimed range of 40-95 % by weight of the HPC is obvious as within the ordinary skill of the art, but the applicants would argue that while it may be obvious to try other levels of the release-controlling cellulose, Jenkins' use of 2-15 % by weight for the water soluble hydroxyalkyl cellulose (or even 4-30 % if one were to add the levels of the matrix and the coating of Jenkins) does not suggest the presently-claimed level of 40-95 % by weight as presently claimed, and the examiner has presented no rationale for why it would be obvious to use the higher level.

The examiner's characterization of the Arwidsson invention is misleading, as it omits the key element, the solid core.

The examiner states that Jenkins teaches an orally administrable pharmaceutical composition comprising the same ingredients, in similar amounts with a similar intended purpose as the applicant. This characterization is over-broad. The Jenkins composition is intended to be used in the mouth, while the presently claimed composition is intended to be ingested. The ingredients of Jenkins would be the same as the HPC employed by the applicants only if Jenkins

selected HPC for both his matrix and his extragranular mucosa-adhesive cellulose, but he lists several materials which may be employed for each of these items. The relative amounts of ingredients in Jenkins and the present inventions are in fact different. Finally, the intended purposes are different, though both are intended for controlled release of a drug; Jenkins' purpose is to release the drug into the bloodstream via the mucosa, while the applicant's purpose it to release the drug in a controlled manner into the GI tract, from which it is absorbed into the body.

The examiner argues that the applicants' use of the word "comprising" in their claim language would permit the exclusion or inclusion of additional ingredients. "Comprising" language permits the inclusion of additional elements, but not the exclusion of additional elements, as the examiner should be aware. In the present amendment, "comprising" language in claims 1 and 12 has been revised to read "consisting essentially of".

The examiner states in conclusion that there is no significant difference between the prior art and the instant invention since the combination of active compounds with hydrophilic polymers is clearly exhibited by both the Jenkins and Arwidsson references. This conclusion is unreasonable. That there are differences between the art and the present invention will be fully developed below, and the fact that both the prior art references and the present invention relate to combinations of an active compound and hydrophilic polymers does not equate to obviousness without a suggestion to make the changes to the teachings of the prior art which would be necessary to arrive at the presently claimed invention. There are no such suggestions here.

Discussion of the cited references

The two Jenkins references are essentially the same, and will not be discussed separately here. Jenkins discloses a buccal tablet intended for use in the oral or nasal cavity, and not for ingestion. Also disclosed is a method for making such tablets.

The tablet of Jenkins is formed of granules composed of a higher aliphatic alcohol, a hydrated water soluble hydroxyalkyl cellulose, and a drug distributed throughout this matrix,

each granule being coated with a cellulose derivative which is adherent to the mucosa (termed "extragranular mucosa-adhesive cellulose"), the coated granules being compressed together into the final tablet form. The extragranular mucosa-adhesive cellulose may be any of several listed materials, preferably hydroxypropylcellulose (HPC); it has a numerical average molecular weight above 200,000 and preferably above 500,000, and is employed at a level of 2-15 % by weight of the total dosage form weight. The hydroxyalkyl-cellulose constituent of the interior of the granules may be any of several listed materials including hydroxypropylcellulose, and preferably is hydroxyethylcellulose (HEC); it is employed at a level of 2-15% by weight of the total dosage form weight. The higher aliphatic alcohol constituent of the granules may be any of several listed materials, contains 8-18 carbons, and is employed in the granules at a level of 5-35% by weight of the total dosage form weight. Prior to compression of the coated granules into the final tablet form, the coated granules preferably have a granule size of less than 1000μm (1 mm), and more preferably less than 100μm (0.1 mm).

Jenkins' process for making his buccal tablets comprises a) forming granules comprising an orally administerable drug, a higher aliphatic alcohol of 8-18 carbon atoms and hydrated water soluble hydroxyloweralkyl cellulose, b) coating the granules with a cellulose derivative which is adherent to the mucosa, and c) compressing the mucosa adhesive cellulose coated granules to give a solid unit dosage form. See claim 17.

Jenkins' buccal tablets are intended to adhere to the mucosa of the oral or nasal cavities, especially the buccal cavity (the mouth). They are not intended to be ingested. The specification states at column 1, lines 28-33, "A particular problem associated with the buccal administration of drugs, however, is that the oral vehicle containing the drug tends, after a period of time, to become detached from the mucosa. At best this can be merely inconvenient, at worst it may lead to the patient swallowing the vehicle."

The Arwiddson reference discloses controlled release beads containing an inert and non-soluble core of glass or sand particles or a soluble core such as sugar spheres, capable of withstanding mechanical stress. The core is coated with a layer of a hydrophilic polymer which contains an active substance, and this is in turn coated with a release-controlling membrane. The

hydrophilic polymer may be any of several listed materials, including hydroxypropylcellulose (HPC). The cores have a size of 0.1-2 mm, preferably smaller. The ratio of active substance to hydrophilic polymer, and the ratio of active substance to inert non-soluble core are given. The reference states (column 2, lines 45-53) that the controlled release beads of the invention have favorable mechanical properties withstanding cracking, especially of the release controlling membrane, when exposed to mechanical stresses, e.g. during filling in capsules or sachets or during compaction.

The Arwiddson reference claims a process for preparation of the controlled release beads comprising the steps of a) dispersing the active ingredient having a particle size of less than 100 μm in a solution of a hydrophilic polymer, b) spraying a first layer of the dispersal of active ingredient in hydrophilic polymer onto the insoluble inert core unit or multiple thereof, and c) spraying the outer membrane for controlled release onto the first layer. See claim 8.

Comparison of the art and the present invention

In Jenkins, the granules contain the active ingredient, plus a higher aliphatic alcohol and a hydrated water soluble hydroxycellulose, and are coated with an "extragranular mucosa-adhesive cellulose". The granules are compacted into tablets.

By contrast, in the present invention the sustained-release particles contain active ingredient plus hydroxypropyl cellulose of a specified molecular weight and molar degree of substitution, but do not contain a higher aliphatic alcohol, and are not further coated. The particles are employed in capsules or sachets, or only lightly compacted so that the resulting tablet rapidly degrades back into the particles in the body.

In Arwidsson, the controlled release beads must contain a solid core, a layer of active ingredient plus hydrophilic polymer, plus an additional outer control release membrane.

By contrast, in the present invention, the sustained-release particles do not require the solid core or the additional control release membrane layer of Arwidsson.

Argument against obviousness

There is no suggestion to modify the disclosure of Jenkins to arrive at the presently claimed invention. To do so would require deleting the higher aliphatic alcohol from the granule composition, deleting the external coating of a "mucosa-adhesive cellulose" on the granules, recognizing that the water soluble hydroxyalkyl cellulose of the granule composition should have a molecular weight of 250,000 to 1,200,000 and a molar degree of substitution of at least 3, and changing the relative amounts of the materials. The art does not suggest the combination of these changes.

There is no suggestion to modify the disclosure of Arwidsson to arrive at the presently claimed invention. To do so would require deleting the solid core which is the key to the Arwidsson invention, and deleting the outer controlled release membrane on the beads. The art makes no such suggestions.

To arrive at the presently-claimed multi-unit sustained release dose form from a combination of the Jenkins and Arwidsson disclosures, one would have to make particles containing active ingredient plus hydroxypropyl cellulose (the soluble hydroxyalkyl cellulose of Jenkins and the hydrophilic polymer of Arwidsson) plus active ingredient, but without the solid core of Arwidsson and without the higher aliphatic alcohol of Jenkins. The hydroxypropyl cellulose would have to have a molecular weight of 250,000 – 1,200,000 and a molar degree of substitution of at least 3. The amount of the HPC would have to be 40 – 90% by weight of the mixture of HPC and active ingredient. The art does not suggest such a combination of changes.

To arrive at the presently-claimed process for producing an orally administratable multiple-unit sustained-release pharmaceutical composition having controlled agitation-independent release from a combination of Jenkins and Arwidsson, one would first have to form particles which contain active ingredient plus from 40 to 95% by weight of hydroxypropyl cellulose which has a molecular weight of 250,000 – 1,200,000 and a molar degree of substitution of at least 3, but which do not contain the higher aliphatic alcohol of 8-18 carbons of Jenkins, and which do not contain the inert core of Arwidsson. Next, one would incorporate

these particles into an orally administratable multi-unit sustained release dose form directly, without employing Jenkins' step of applying a coating of a cellulose derivative which is adherent to the mucosa, and without employing Arwidsson's step of spraying an outer membrane for controlled release. The art does not suggest this combination of changes.

Jenkins teaches away from the particles of active ingredient plus hydroxypropyl cellulose of the present invention by its teaching that "This extragranular [mucosa-adhesive cellulose] coating is to be differentiated from intragranular cellulose which is distributed through the body [the final sustained release tablet] but which may or may not provide sufficient surface coating for good adherence of the body to the mucosa. Thus, the extragrannular mucosa-adhesive cellulose of the present invention improves the attachment of the dosage form to the oral or nasal mucosa, especially within the buccal cavity. ..... It has surprisingly been found that by employing extragranular cellulose adhesive, especially powdered adhesive, the adherent properties of the resulting dosage form are significantly greater than those of a dosage form having intragranular adhesive only." See the specification at column 1, line 62 through column 2, line 13.

The Arwidsson reference also teaches away from the particles of active ingredient plus hydroxypropyl cellulose of the present invention by its teaching that the particles should possess a solid core, as well as an outer release controlling membrane. "Multiple unit dosage systems may be filled into capsules or sachets, thus requiring sufficient mechanical properties to withstand processing. It may even be advantageous to compact multiple units into tablets, subjecting the systems to significant mechanical stress. According to the present invention the problem of mechanical suitability mentioned above has been overcome by using inert and non-soluble cores of glass or sand particles or soluble cores such as sugar spheres capable of withstanding mechanical stress, in combination with a plasticizing layer of a hydrophilic polymer containing the active substance, optionally with additional layers of the polymer not containing the active substance, layered between the core and the release controlling membrane." See the specification at column 1, lines 26-40.

In view of the above amendments and arguments, this application is deemed to be in condition for allowance, and allowance is accordingly requested.

Respectfully submitted,

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